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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOODWARD, CHERIE MICHELLE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,295	BHASKARAN ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-164* is/are pending in the application.

4a) Of the above claim(s) *1-37,73 and 77-164* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-72 and 74-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :9/28/04,12/10/04,12/22/04,3/23/05,10/18/05.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 38-76, in the reply filed on 30 June 2006 is acknowledged. The traversal is on the grounds that the subject matter of the groups are directed to similar overlapping subject matter and that examination of the entire application can be made without serious burden, even though it includes claims to independent or distinct inventions. Applicant argues that at least Groups I and II should be examined together because they are directed to methods of synthesizing conjugates of one or more synthetic water-soluble polymers with a cytokine, chemokine, growth factor, or a polypeptide hormone, or an antagonist thereof. This is not found persuasive because Group I is drawn to method claims, while Group II is drawn to product claims. Product and process inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, any of the multiple products can be made by the process of Group I. Alternatively, the products of Group II may be made by other methods, which are well known in the art (see below). As such, the methods of Group I are independent or distinct from the products of Group II.

Claim 73 is withdrawn from Group II and placed in Group I, as claim 73 is dependent on claim 37, which is part of Group I.

Because the examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to**

do so may result in a loss of the right to rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

At the present time, no product claims are found to be allowable. The requirement is still deemed proper and is therefore made FINAL.

Formal Matters

2. Claims 1-164 are pending. Claims 1-37, 72, and 77-164 are withdrawn as being drawn to non-elected inventions. Claims 38-72 and 74-76 are under examination. Claim

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 9/28/2004, 12/10/2004, 12/22/2004, 3/23/2005, and 10/18/2005 have considered by the examiner. Signed copies are attached hereto.

Item AS in the IDS submitted 12/10/2004 has not been considered because it is an unverified partial translation of a foreign document. As such, the AS reference fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Similarly, the copy of the co-pending, unpublished Taiwanese application listed as Item AR (page 5 of 5) and item AP4 (page 4 of 36), and item AF8 (page 7 of 36) in the IDS filings of 28 September 2004 have not been considered because the document are not in English and no translation has been provided. The references will be considered when copies of a certified translation of the entire documents are received.

Objections - Specification

4. The use of the trademarks TOYOPEARL (p. 72) and SUPERDEX (pp. 72 and 75) have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Obviousness-Type Double Patenting Rejections

5. Claims 38-72, and 74-76 are provisionally rejected on the ground of nonstatutory double patenting over claims 21-24 and 29-49 of copending Application No. 10/743,068, filed 23 December 2003; claims 1-38, 60-86, and 94-95 of copending Application No. 10/669,597, filed 25 September 2003. These claims render obvious or are rendered obvious by the instant claims. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: conjugates comprising bioactive components attached to a polymer.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 38 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PEGylatyed-IFNα, PEGylated-IL-2, PEGylated-EGF, and PEGylated-IGF-1, does not reasonably provide enablement for all conjugates comprising cytokines, chemokines, growth factors, polypeptide hormones, or antagonists thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a conjugate comprising a cytokine, a chemokine, a growth factor or a polypeptide hormone, or antagonist thereof, coupled to one or more synthetic water-soluble polymers, wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected for its membership in the group of receptor-binding proteins and polypeptides in which the amino-terminal amino acid is located remotely from one or more receptor-binding domains and wherein said one or more polymers is/are coupled to said amino-terminal amino acid. The nature of the invention is drawn to PEGylated cytokine/chemokine/growth factor conjugates.

The state of the prior art is such that PEGylation of proteins is well known, the first patent having been granted to Davis et al., in 1979 (US Patent 4,179,337, issued 18 December 1979, benefit to 20 July 1973). It is well know that PEGylation of proteins increases the half-life of the proteins, reduces their degradation and antigenicity, thus making PEGylated proteins useful for therapeutic purposes. However, polymer moieties can be attached at various locations on a protein and the moieties can be of various sizes, from a single amino acid (i.e. MET-RANTES) (see e.g., Elsner et al., Eur J Immunol. 1997 Nov;27(11):2892-8, Abstract only) to an organic moiety (i.e. Aminooxypentane-RANTES, also called AOP-RANTES) (see e.g., Mack et al., J Exp Med. 1998 Apr 20;187(8):1215-24, Abstract only) and can stericly hinder receptor sites, three-dimensional structure of proteins, or alter biological activities of the protein (see i.e. Delgado et al., Crit Rev Ther Drug Carrier Syst. 1992;9(3-4):249-304, Abstract only).

Conservation of biological activity is highly dependent on the coupling techniques used (see, for example, Francis et al., Int J Hematol. 1998 Jul;68(1):1-18, Abstract only).

The level of skill of those in the art is high due to the complex nature, interrelatedness, and negative regulatory functions of cytokines, chemokines, and growth factors, which may act in an autocrine, paracrine, or endocrine manner, depending on the cytokine and the species, as well as the intricacies of the pathoimmunology related to the complexities of immune function.

There are five working examples of PEGylated conjugates. Example 1 discloses PEG-IFN-α. Example 2 discloses PEG-IL-2. Examples 3 and 4 disclose PEG-EGF and PEG-IGF-1. Example 5 discloses PEG-IFN-β, PEG-EGF, PEG-FGF-2, PEG-IGF-1, and PEG-INF-γ. The art also teaches how to make and use a number of PEGylated moieties (see *supra*, and in the art recited below).

General guidance is given regarding how to make and test variants of any protein. However, the scope of the patent protection sought by Applicant as defined by the claim fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons. The problem of predicting protein structure from sequence data known in the art and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al, 1990, *Science* 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, *Biochemistry* 29:8509-8517). However, Applicant has provided little or no guidance beyond the mere presentation of laboratory names of cytokines/chemokines/growth factors/and polypeptide hormones to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by additions of polymer moieties), and the nature and extent of changes that can be made in these positions without affecting biological function of the cytokines/chemokines/growth factors/and polypeptide hormones or antagonists. Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Applicants have not taught how to make or use the full scope of the genera of cytokines, chemokines, growth factors, polypeptide hormones, or antagonists thereof, such that the biological activity of the members of genera can be determined without undue experimentation. Further, the genus of "antagonists thereof" is excessively broad and encompasses any number of proteins, nucleic acids, and small molecules that antagonize any cytokine, chemokine, growth factor, polypeptide hormone of any species. No species of antagonist are described in the disclosure.

Additionally, although general structural information is given regarding the claimed conjugates, no functional guidance is provided, such that one of skill in the art would know whether the claimed species of conjugates within the claimed genera of conjugates for cytokines, chemokines, growth factors, polypeptide hormones, or antagonists thereof are biologically functional without having to engage in undue experimentation. It is accepted in the art that conservation of biological activity is highly dependent on the coupling techniques used in the PEGylation process (see, i.e., Francis et al., Int J Hematol. 1998 Jul;68(1):1-18, Abstract only). The vast number of potential conjugates claimed and the lack of guidance provided in the art and in the instant disclosure, as to the structure or function of the claimed general of conjugates, makes both the structure and biological function of the claimed conjugates unpredictable. As such, undue experimentation would be required to make and use the conjugates as claimed.

The breadth of the claims is excessive. For example, claim 39 recites the conjugate of claim 38 wherein said one or more polymers are selected from the group consisting of one or more poly(amino acids). The claim reads on all conjugates of any polypeptide comprising two or more amino acids with any cytokine, chemokine, growth factor, polypeptide hormone, or antagonist thereof of any species. Applicant has not taught how make or use a sufficient number of polypeptide conjugates such that the skilled artisan would know how to make or use the claimed invention without engaging in undue experimentation to determine the structure of any one or more poly(amino acids) conjugated to any cytokine, chemokine, growth factor, polypeptide hormone, or antagonist thereof. Further, Applicants' claims are also excessively broad because of the limited number of exemplary conjugates taught in the disclosure and the vast numbers of cytokines, chemokines, growth factors, fragments, variants, and antagonists of various species that fall within the claims, as written.

Therefore, based on the discussions above concerning the art's recognition that biological function of a PEGylated conjugate cannot be assumed and is highly dependent on the coupling techniques used, the specification fails to teach the skilled artisan how to make or use the claimed invention without resorting to undue experimentation.

Due to the large quantity of experimentation such that it can be determined how to make or use the claimed conjugates, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological function cannot be determined from the structure of the conjugate alone, and the breadth of the claims which fail to recite more than a few particular structural conjugates without any guidance regarding functional activity, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

8. Claims 38, 40-45 and 68-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PEGylatyed-IFNα, PEGylated-IL-2, PEGylated-EGF, and PEGylated-IGF-1, does not reasonably provide enablement for muteins, antagonists, variants, analogs, mimics, or derivatives of M-CSF, GM-CSF, LIF, TPO, EPO, SCF, Flt 3 ligand, OSM, IL-2, IL-3, IL-4, IL-5, IL-6, IL7, IL-9, IL-10, IL-11, IL-12(p35), IL-13, IL-15, IL-17, IFN-α, IFN-β, consensus interferon, prolactin, growth hormone, nonglycosylated EPO, EPO, TNFα, IL-1α, IL-1β, IL-12(p40), IL-16, EGF, FGF-1, FGF-2, FGF-4, KGF/FGF-7, NAP-2, SDF-1α, IL-8, MCP-1, MCP-2, MCP-3, eotaxin-1, eotaxin-2, eotaxin-3, RANTES, MPIF-1, neurotactin, MIF, GRO-α/MGSA), or any cytokine, chemokine, or growth factor from any species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims recite as stated, *supra*. The instant disclosure fails to provide any guidance regarding the structure or function of any muteins, antagonists, variants, analogs, mimics, or derivatives of the above recited cytokines, chemokines, and growth factors, or antagonists thereof. It is accepted in the art that conservation of biological activity is highly dependent on the coupling techniques used in the PEGylation process (see, i.e., Francis et al., Int J Hematol. 1998 Jul;68(1):1-18, Abstract only). The vast number of potential conjugates, mutiens, antagonists, variants, analogs, mimics, and derivatives claimed and the lack of guidance provided in both the art and in the instant disclosure, as to the structure or function of the claimed general of conjugates, makes both the structure and biological function of the claimed conjugates unpredictable. As such, undue experimentation would be required to make and use the conjugates as claimed.

The breadth of the claims is excessive because of the limited number of exemplary conjugates taught in the disclosure and the vast numbers of cytokines, chemokines, growth factors, fragments,

variants, and antagonists of various species that fall within the claims, as written, and the fact that no muteins, antagonists, variants, analogs, mimics, or derivatives are taught at all.

The specification does not teach which amino acid residues or regions of the claimed genera of cytokines, chemokines, and growth factors, or antagonists thereof, can be mutated or replaced to create a cytokine, chemokine, growth factor, or antagonist thereof, that can be conjugated and still retain biological activity. Furthermore, a person of ordinary skill in the art would not be able to predict which of the many possible muteins, variants, analogs, or derivates, when conjugated to a water-soluble polymer, would retain the desired biological activity. Such a determination would require further undue experimentation, and therefore the person of ordinary skill would not be able to make and use a conjugate comprising a mutein, variant, analog, or derivate conjugate of any cytokine, chemokine, growth factor, or antagonist thereof.

Therefore, based on the discussions above concerning the art's recognition that biological function of a PEGylated conjugate cannot be assumed and is highly dependent on the coupling techniques used, the specification fails to teach the skilled artisan how to make or use the claimed invention without resorting to undue experimentation.

Due to the large quantity of experimentation such that it can be determined how to make or use the claimed conjugates, muteins, antagonists, variants, analogs, mimics, or derivatives thereof, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological function cannot be determined from the structure of the conjugate alone, and the breadth of the claims which fail to recite more than a few particular structural conjugates without any guidance regarding functional activity and entirely fail to provide guidance on any muteins, antagonists, variants, analogs, mimics, or derivatives, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

9. Claim 72 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence

of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claim recites a pharmaceutical composition comprising the conjugate of claim 38 and a pharmaceutically acceptable carrier or excipient.

When the term "pharmaceutical" is used in the preamble of a claim, its intended use as a pharmaceutical must be shown. The intended use of the claim as a pharmaceutical is imputed to mean every intended use, including use as a preventative, because the claim, as written, fails to limit any such intended use.

The specification does not reasonably provide enablement for prophylaxis (prevention) of any disease in any species by administration of the pharmaceutical of claim 72 by any means. The skilled artisan cannot envision the prevention of any disease by administration of the pharmaceutical of claim 72 by any means. Prevention involves "attacking" the underlying cause of disease; i.e., disrupting the mechanisms which give rise to the disease. The skilled artisan is aware that the causes and/or etiology of all diseases or even the genera of cytokine/chemokine/growth factor – involved diseases were unknown at the time of the invention herein. For purposes of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention. In this case, the specification must disclose a means of preventing cytokine/chemokine/growth factor – involved diseases, regardless of the underlying cause(s). The teachings of the specification do not enabled a person of ordinary kill in the art to make and use the claimed method of prophylaxis. Moreover, "[p]atent protection is granted only in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." Genentech Inc. v. Novo Nordisk A/S, 108 F.3d at 1366, 42 USPQ2d at 1005 (Fed. Cir.), cert. denied, 118 S. Ct. 397 (1997), ("Tossing out the mere germ of an idea does not constitute an enabling disclosure").

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

10. Claim 38 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the

Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite a conjugate comprising a cytokine, a chemokine, a growth factor or a polypeptide hormone, or antagonist thereof, coupled to one or more synthetic water-soluble polymers, wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected for its membership in the group of receptor-binding proteins and polypeptides in which the amino-terminal amino acid is located remotely from one or more receptor-binding domains and wherein said one or more polymers is/are coupled to said amino-terminal amino acid.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., conjugates comprising cytokines, chemokines, growth factors, polypeptide hormones, or antagonists thereof.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There are a few species of the claimed genus disclosed that are within the scope of the claimed genus, *i.e.* PEGylatyed-IFNα, PEGylated-IL-2, PEGylated-EGF, and PEGylated-IGF-1. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. Moreover, the genus of "antagonists thereof" is excessively broad and encompasses proteins, nucleic acids, small molecules, etc. No species of antagonist are described in the disclosure.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which are conjugates comprising cytokines, chemokines, growth factors, polypeptide hormones, or antagonists thereof. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

11. Claims 38, 40-45 and 68-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite as stated, supra. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., conjugates comprising muteins, antagonists, variants, analogs, mimics, or derivatives of M-CSF, GM-CSF, LIF, TPO, EPO, SCF, Flt 3 ligand, OSM, IL-2, IL-3, IL-4, IL-5, IL-6, IL7, IL-9, IL-10, IL-11, IL-12(p35), IL-13, IL-15, IL-17, IFN-α, IFN-β, consensus interferon, prolactin, growth hormone, nonglycosylated EPO, EPO, TNFα, IL-1α, IL-1β, IL-12(p40), IL-16, EGF,

FGF-1, FGF-2, FGF-4, KGF/FGF-7, NAP-2, SDF-1α, IL-8, MCP-1, MCP-2, MCP-3, eotaxin-1, eotaxin-2, eotaxin-3, RANTES, MPIF-1, neurotactin, MIF, GRO-α/MGSA), or any cytokine, chemokine, or growth factor from any species.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

There are a few species of the claimed genus disclosed that are within the scope of the claimed genus, *i.e.* PEGylatyed-IFNα, PEGylated-IL-2, PEGylated-EGF, and PEGylated-IGF-1. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. There are a limited number of exemplary conjugates described in the disclosure. However, there are vast numbers of cytokines, chemokines, growth factors, muteins, antagonists, variants, analogs, mimics, and derivatives that are claimed but not described at all.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which are conjugates comprising muteins, antagonists, variants, analogs, mimics, or derivatives of M-CSF, GM-CSF, LIF, TPO, EPO, SCF, Flt 3 ligand, OSM, IL-2, IL-3, IL-4, IL-5, IL-6, IL7, IL-9, IL-10, IL-11, IL-12(p35), IL-13, IL-15, IL-17, IFN-α, IFN-β, consensus interferon, prolactin, growth hormone, nonglycosylated EPO, EPO, TNFα, IL-1α, IL-1β, IL-12(p40), IL-16, EGF, FGF-1, FGF-2, FGF-4, KGF/FGF-7, NAP-2, SDF-1α, IL-8, MCP-1, MCP-2, MCP-3, eotaxin-1, eotaxin-2, eotaxin-3, RANTES, MPIF-1, neurotactin, MIF, GRO-α/MGSA), or any cytokine, chemokine, or growth factor from any species. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Claim Rejections - 35 USC § 112, Second Paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 38-72, and 74-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite a conjugate comprising a cytokine, chemokine, growth factor, or polypeptide hormone, or antagonist thereof coupled to one or more synthetic water-soluble polymers. The claimed antagonists have structures and functions that are mutually exclusive from the structure and functions of the claimed cytokine/chemokine/growth factor/polypeptide hormone conjugates. Applicant's definition of "antagonist" in the specification (p. 19) fails to clarify this mutual exclusivity. Because the claimed antagonists have structures and functions are mutually exclusive of the claimed conjugates, the intended function of the claimed invention is unclear from the claims, as written.

14. Claims 55 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the conjugate of claim 38, wherein said polymer is coupled to a chemically reactive side chain group. Because almost any molecule can be "chemically reactive" under the right conditions, and the nature of the reaction is not defined by the claims, the metes and bounds of the term "chemically reactive" are not adequately defined by the claims or the disclosure.

15. Claim 71 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the conjugate of claim 38, wherein the coupling of said polymer to said cytokine, chemokine, growth factor, or polypeptide hormone, or antagonist thereof, at said amino-terminal amino acid "mimics" the "beneficial effects" of glycosylation or hyperglycoslations of said cytokine... The meaning of the word "mimics" is not defined by the claim or the specification and could be interpreted as exactly reproducing the effect of glycosylation or reproducing the effects of glycosylation to a certain degree or extent that is not specified in the claim or the disclosure. As such, the metes and bounds of the term "mimics" are not adequately defined. Further, neither the claims nor the disclosure define the "beneficial effects" of glycosylation or hyperglycosylation. It is well known in the art that many cytokines, which are also glycoproteins, can be stripped of their posttranslational moieties and still retain function (see, for exemplary purposes, Goochee et al., Biotechnology, 1991 Dec 9:1347-1355, especially at 1351, column 1, last paragraph). As such, the metes and bounds of the term "beneficial effects" are not adequately defined.

16. Claims 74-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The only recited components of the kits are the compositions of claims 38 and 40. The compositions of claims 38 and 40 are not different from one another; claim 40 is dependent on claim 38. Further, although the disclosure recites other components that may be part of a kit, the limitations of the specification may not be read into the claims. The claims are also objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

18. Claims 38-43, 46-48, 51, 53-57, 61-63, 65, 69, 71-72, and 74-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Hiratani, US Patent 4,609,546 (2 September 1986).

The claims recite a conjugate comprising a cytokine, a chemokine, a growth factor or a polypeptide hormone, or antagonist thereof, coupled to one or more synthetic water-soluble polymers, wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected for its membership in the group of receptor-binding proteins and polypeptides in which the amino-terminal amino acid is located remotely from one or more receptor-binding domains and wherein said one or more polymers is/are coupled to said amino-terminal amino acid; wherein said one or more polymers is/are selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a four helix bundle structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited

group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a .beta.-sheet or .beta.-barrel structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine is an IL-2; wherein said cytokine is an interferon-alpha; wherein said growth factor is EGF; wherein said polymer is covalently coupled to the alpha amino group of said amino-terminal amino acid; wherein said covalent coupling of said polymer to said alpha amino group is via a secondary amine linkage; wherein said polymer is coupled to a chemically reactive side chain group of said amino-terminal amino acid; wherein said reactive side chain is selected from the recited group; wherein said water-soluble polymer is a polyalkylene glycol; wherein said polyalkylene glycol is selected from the group consisting of a poly(ethylene glycol), a monomethoxypoly(ethylene glycol) and a monohydroxypoly(ethylene glycol); wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 100 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 5 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 10 kDa and about 20 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 12 kDa and about 30 kDa, inclusive; wherein said polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein the coupling of said polymer to said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, at said amino-terminal amino acid mimics the beneficial effects of glycosylation or hyperglycosylation of said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof; a pharmaceutical composition comprising the conjugate of claim 38 and a pharmaceutically acceptable carrier or excipient; a kit comprising the pharmaceutical composition of claim 37; a kit comprising the conjugate of claim 38; a kit comprising the conjugate of claim; a kit comprising the pharmaceutical composition of claim 72.

Hiratani teaches conjugation of polyalkylene glycols, specifically polyoxyethylene-polyoxyproplene copolymer to human physiologically active polypeptides or glycoproteins (column 1, lines 7-10), including EGF, growth hormone, IFNα, IFNβ, and IL-2 (column 1, lines 65 to column 2, line 3). Conjugation of the active substances to the copolymer through the N-terminal primary amino group and/or the secondary ε-amino groups are taught at column 2, lines 22-25). The polyoxyethylene-polyoxyproplene copolymers are taught as having molecular weights ranging from about 1 kDa to about 14 kDa (column 1, lines 39-40). Pharmaceutical compositions are taught at claims 10-13. Kits comprising microplates are taught at column 4, Example 3, line 36.

19. Claims 38-43, 46-48, 53-58, 61-67, 69, 71, and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Minami et al., US Patent 5,037,969 (6 August 1991).

The claims recite a conjugate comprising a cytokine, a chemokine, a growth factor or a polypeptide hormone, or antagonist thereof, coupled to one or more synthetic water-soluble polymers, wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected for its membership in the group of receptor-binding proteins and polypeptides in which the amino-terminal amino acid is located remotely from one or more receptor-binding domains and wherein said one or more polymers is/are coupled to said amino-terminal amino acid; wherein said one or more polymers is/are selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a four helix bundle structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a .beta.-sheet or .beta.-barrel structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine is an IL-2; wherein said cytokine is an interferon-alpha; wherein said growth factor is EGF; wherein said polymer is covalently coupled to the alpha amino group of said amino-terminal amino acid; wherein said covalent coupling of said polymer to said alpha amino group is via a secondary amine linkage; wherein said polymer is coupled to a chemically reactive side chain group of said amino-terminal amino acid; wherein said reactive side chain is selected from the recited group; wherein said water-soluble polymer is a polyalkylene glycol; wherein said polyalkylene glycol is selected from the group consisting of a poly(ethylene glycol), a monomethoxypoly(ethylene glycol) and a monohydroxypoly(ethylene glycol); wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 100 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 5 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 10 kDa and about 20 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 18 kDa and about 60 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 12 kDa and about 30 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of about 20 kDa; wherein said polyalkylene glycol has a molecular weight of about 30 kDa; wherein said polypeptide hormone, or antagonist thereof, is selected from growth hormone; wherein the coupling of said polymer to said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, at said amino-terminal amino acid mimics the beneficial effects of glycosylation or hyperglycosylation of said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof; and a

pharmaceutical composition comprising the conjugate of claim 38 and a pharmaceutically acceptable carrier or excipient.

Minami et al., teach conjugation of polyalkylene glycols, specifically PEG with modified sugar moieties (column 1, lines 59-66), to natural and recombinant cytokines and hormones, including EGF, growth hormone, IFNα, IFNβ, and IL-2 (column 5, lines 5-14). Conjugation of the cytokines and hormones to the sugar-moiety-modified PEG through direct bonding to the N-terminal primary amino group and/or the secondary ε-amino groups are taught at column 6, lines 63-68 to column 7, lines 1-5). The sugar-moiety-modified PEGs are taught as having molecular weights ranging from about 5 kDa to about 50 kDa and preferably about 10 kDa to about 30 kDa (column 5, lines 18-20). Pharmaceutical compositions are taught at column 7, lines 18-20.

20. Claims 38-72, and 74-76 are rejected under 35 U.S.C. 102(e) as being anticipated by Martinez et al., US Pregrant Publication US 2004/0062746 A1 (1 April 2004, benefit to 12 December 2002).

The claims recite a conjugate comprising a cytokine, a chemokine, a growth factor or a polypeptide hormone, or antagonist thereof, coupled to one or more synthetic water-soluble polymers, wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected for its membership in the group of receptor-binding proteins and polypeptides in which the amino-terminal amino acid is located remotely from one or more receptor-binding domains and wherein said one or more polymers is/are coupled to said amino-terminal amino acid; wherein said one or more polymers is/are selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a four helix bundle structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a .beta.-sheet or .beta.-barrel structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a mixed .alpha./.beta. structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine is an IL-2; wherein said cytokine is an interferon-alpha; wherein said cytokine is TNF-alpha; wherein said cytokine antagonist is a TNF-alpha Antagonist; wherein said growth factor is EGF; wherein said growth factor is IGF-1; wherein said polymer is covalently coupled to the alpha amino group of said amino-terminal amino acid; wherein said covalent coupling of said polymer to said alpha amino group is via a secondary amine linkage; wherein

said polymer is coupled to a chemically reactive side chain group of said amino-terminal amino acid; wherein said reactive side chain is selected from the recited group; wherein said water-soluble polymer is a polyalkylene glycol; wherein said polyalkylene glycol is selected from the group consisting of a poly(ethylene glycol), a monomethoxypoly(ethylene glycol) and a monohydroxypoly(ethylene glycol); wherein said polyalkylene glycol is a monomethoxypoly(ethylene glycol); wherein said polyalkylene glycol is a monohydroxypoly(ethylene glycol); wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 100 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 5 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 10 kDa and about 20 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 18 kDa and about 60 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 12 kDa and about 30 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of about 20 kDa; wherein said polyalkylene glycol has a molecular weight of about 30 kDa; wherein said polypeptide hormone, or antagonist thereof, is selected from the group consisting of prolactin and prolactin analogs that mimic or antagonize the biological effects of prolactin that are mediated by prolactin receptors; wherein said polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein the coupling of said polymer to said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, at said amino-terminal amino acid mimics the beneficial effects of glycosylation or hyperglycosylation of said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof; a pharmaceutical composition comprising the conjugate of claim 38 and a pharmaceutically acceptable carrier or excipient; a kit comprising the pharmaceutical composition of claim 37; a kit comprising the conjugate of claim 38; a kit comprising the conjugate of claim; a kit comprising the pharmaceutical composition of claim 72.

Martinez et al., (2004/0062746) teach conjugation of polyalkylene glycols, specifically PEG, and more specifically, monomethoxypolyethyleneglycol and monohyoxypolyethyleneglycol to the N-termini of IL-2, IL-8, IFNα, IFNβ, EPO, TNF, EGF, growth hormone, prolactin, and antagonists thereof (paragraphs 28-31, 67-72, and 82). Insulin-like growth factors are taught in claims 30 and 85. Polymers of various molecular weights are taught including about 1 kDa to about 100 kDA, 2 kDa to about 60 kDa, about 2 kDa to about 30 kDa, about 5 kDa to about 20 kDa, about 10 kDa to about 20 kDa, about 18 kDa to about 60 kDa, about 20 kDa, to about 30 kDa, about 20kDa, and about 30 kDa (paragraphs 73 and 76). Pharmaceutical compositions are taught at paragraphs 121-123. Numerous polymers suitable for

conjugation including PEG, monomethoxyPEG, and monohydroxyPEG, are taught at paragraphs 28-31, 67-72 160 (Example 1), and 184 (Example 7). Kits are taught at paragraph 157.

21. Claims 38-72, and 74-76 are rejected under 35 U.S.C. 102(e) as being anticipated by Martinez et al., US Pregrant Publication US 2004/0062748 A1 (1 April 2004, benefit to 30 September 2002).

The claims recite as discussed *supra*. Martinez et al., (2004/0062748) teach conjugation of polyalkylene glycols, specifically PEG, and more specifically, monomethoxypolyethyleneglycol and monohyoxypolyethyleneglycol to the N-termini of IL-2, IL-8, IFNα, IFNβ, EPO, TNF, EGF, growth hormone, prolactin, and antagonists thereof (paragraphs 29, 30, 70, and 82). Insulin-like growth factors are taught in claims 30 and 85. Polymers of various molecular weights are taught including about 1 kDa to about 100 kDA, 2 kDa to about 60 kDa, about 2 kDa to about 30 kDa, about 5 kDa to about 20 kDa, about 10 kDa to about 20 kDa, about 18 kDa to about 60 kDa, about 20 kDa, to about 30 kDa, about 20kDa, and about 30 kDa (paragraphs 73 and 76). Pharmaceutical compositions are taught at paragraphs 121-123. Numerous polymers suitable for conjugation including PEG, monomethoxyPEG, and monohydroxyPEG, are taught at paragraphs 29, 30, 67, 70, 71, 76, 160 (Example 1), and 186 (Example 7). Kits are taught at paragraph 158.

22. Claims 38-41, 46, 48, 70-72, and 74-76 are rejected under 35 U.S.C. 102(e) as being anticipated by Lin et al., US Pregrant Publication US 2005/0107277 (15 May 2005 benefit to 18 January 2002).

The claims recite as discussed *supra*. Specifically, the claims are drawn to a cytokine conjugate comprising IFNα or IFN-β and polyalkylene glycols, pharmaceutical compositions comprising the conjugate interferons, and a kit.

Lin et al., teach conjugation of polyalkylene glycols, specifically PEG, and more specifically, monomethoxypolyethyleneglycol, to the N-termini of IFNα, IFN-β and IFN-γ peptides (paragraphs 559-561, Example 2, and paragraphs 649-677) and pharmaceutical compositions of said conjugates with one or more pharmaceutically acceptable excipients or carriers (paragraphs 264, 575, and 576). Lin et al., teach that a number of polypeptides can be conjugated to PEG, including all forms of interferon, naturally occurring or those produced recombinantly. Lin et al., also teach the use of Betaseron, which is known in the art as a non-glycosylated IFN-β-1b polypeptide (paragraphs 12 and 564). Lin et al., also teach the use the IFN-β-PEG conjugate in a 24-well plate (which is read as a kit, according to the definition of a kit in the instant specification, p. 70, paragraph 149) (see, Lin et al., Example 6, paragraph 706).

23. Claims 38-72, and 74-76 are rejected under 35 U.S.C. 102(f) because the Applicant did not invent the claimed subject matter. Co-pending applications 10/743,068 and 10/669597, as well as 10/314,092, now abandoned, have an inventive entity that is different from that of the instant application. The references disclose and claim the instant invention of conjugates comprising bioactive proteins attached to a polyalkylene group. The references both contain and claim subject matter that is identical to, renders obvious, or is rendered obvious by the instant claims. Further, the specifications appear to be largely identical to the instant disclosure. See MPEP 2137.

Claim Rejections - 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

26. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

27. Claims 38-47, 51, 53, 55-59, 61-66, 68-72, and 74-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al., US Patent 4,179,337 (18 December 1979), in view of Drummond et al., WO 99/45026 (published 10 September 1999).

The claims recite a conjugate comprising a cytokine, a chemokine, a growth factor or a polypeptide hormone, or antagonist thereof, coupled to one or more synthetic water-soluble polymers, wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected for its membership in the group of receptor-binding proteins and polypeptides in which the amino-terminal amino acid is located remotely from one or more receptor-binding domains and wherein said one or more polymers is/are coupled to said amino-terminal amino acid; wherein said one or more polymers is/are selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a four helix bundle structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a .beta.-sheet or .beta.-barrel structure; wherein said water-soluble polymer is a polyalkylene glycol; wherein said polyalkylene glycol is selected from the group consisting of a poly(ethylene glycol), a monomethoxypoly(ethylene glycol) and a monohydroxypoly(ethylene glycol); wherein said polyalkylene glycol is a monomethoxypoly(ethylene glycol); wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 100 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 5 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 10 kDa and about 20 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 18 kDa and about 60 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 12 kDa and about 30 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of about 20 kDa; wherein said polyalkylene glycol has a molecular weight of about 30 kDa; wherein said polypeptide hormone, or antagonist thereof, is selected from the group consisting of prolactin and prolactin analogs that mimic or antagonize the biological effects of prolactin that are mediated by prolactin receptors; wherein said polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein the coupling of said polymer to said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, at said amino-terminal amino acid mimics the beneficial effects of glycosylation or hyperglycosylation of said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof; a pharmaceutical composition comprising the conjugate of claim 38 and a pharmaceutically acceptable carrier or excipient; a kit comprising the pharmaceutical composition of claim 37; a kit comprising the conjugate of claim 38; a kit comprising the conjugate of claim; a kit comprising the pharmaceutical composition of claim 72.

Davis et al., teach conjugation of polyalkylene glycols, specifically polyethylene glycol (PEG) (column 2, lines 53-55). PEG-conjugates of prolactin, growth hormone (somatomedin), and EPO are taught at column 3, lines 44-51 and claims 1-2. , MonomethoxyPEG is taught at column 7, line 3. Polymers of various molecular weights are taught including PEG with a molecular weight of about 0.5 kDa to about 20 kDa (column 2, line 57, and claim 1). Pharmaceutical compositions are taught at column 12, line 30 to column 15, line 37, Examples X-XVIII, especially Example 10, where pharmaceutical compositions of prolactin, growth hormone (somatomedin), and EPO are taught (column 12, especially lines 65 to column 13, line 3. Kits comprising PEG-conjugates are taught at column 16, lines 6-10. Davis et al., do not teach polymers coupled to an amino-terminal amino acid of a polypeptide.

Drummond et al., teach conjugation of polyalkylene glycols, including PEG, to the amino-terminal amino acid of polypeptides (pages 3, 14-15, especially Examples 12-13) including IL-2 (page 3), EGF (p. 4), and IL-8 (p. 2). Pharmaceutical compositions are taught at p. 3. PEG polymers with various molecular weights are taught at p. 15, Examples 3 and 4.

It would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Davis et al., and Drummond et al., because Davis et al., teach the successful PEGylation of prolactin, growth hormone, and EPO at the C-terminal of the proteins. Drummond et al., taught the successful PEGylation of IL-2, IL-8, and EGF at the N-terminal amino acid of the polypeptides. The person of ordinary skill in the art would have been motivated to make the modifications because N-terminal PEG additions have better in vivo effects and there is less risk of loss of biological activity of the proteins due to steric interference with binding sited by the attached PEG-moiety. One of skill in the art reasonably would have expected success because Drummond et al., taught the PEGylation of two interleukins and a growth factor under coupling conditions favorable to N-terminal attachment, thus preserving biological function of the conjugate polypeptide.

28. Claims 38-66, 69-72, and 74-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaertnere et al., (Bioconjugate Chem 1996 7:38-44), in view of Ikeda et al., US Patent 5,183,660 (2 February 1993), in further view of Tsutsumi et al (Br J Cancer 1995 May; 71(5)963-8, Abstract only), Seely, US Patent 5,935,564 (10 August 1999, benefit to 6 March 1996), and Gnanou et al., (Makromol Chem. 1987. 188:2111-2119).

The claims recite a conjugate comprising a cytokine, a chemokine, a growth factor or a polypeptide hormone, or antagonist thereof, coupled to one or more synthetic water-soluble polymers, wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is

selected for its membership in the group of receptor-binding proteins and polypeptides in which the amino-terminal amino acid is located remotely from one or more receptor-binding domains and wherein said one or more polymers is/are coupled to said amino-terminal amino acid; wherein said one or more polymers is/are selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a four helix bundle structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a .beta.-sheet or .beta.-barrel structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, has a mixed .alpha./.beta. structure; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine is an IL-2; wherein said cytokine is an interferon-alpha; wherein said cytokine is TNF-alpha; wherein said cytokine antagonist is a TNF-alpha Antagonist; wherein said growth factor is EGF; wherein said growth factor is IGF-1; wherein said polymer is covalently coupled to the alpha amino group of said amino-terminal amino acid; wherein said covalent coupling of said polymer to said alpha amino group is via a secondary amine linkage; wherein said polymer is coupled to a chemically reactive side chain group of said amino-terminal amino acid; wherein said reactive side chain is selected from the recited group; wherein said water-soluble polymer is a polyalkylene glycol; wherein said polyalkylene glycol is selected from the group consisting of a poly(ethylene glycol), a monomethoxypoly(ethylene glycol) and a monohydroxypoly(ethylene glycol); wherein said polyalkylene glycol is a monomethoxypoly(ethylene glycol); wherein said polyalkylene glycol is a monohydroxypoly(ethylene glycol); wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 100 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 1 kDa and about 5 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 10 kDa and about 20 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 18 kDa and about 60 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of between about 12 kDa and about 30 kDa, inclusive; wherein said polyalkylene glycol has a molecular weight of about 20 kDa; wherein said polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, is selected from the recited group; wherein the coupling of said polymer to said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof, at said amino-terminal amino acid mimics the beneficial effects of glycosylation or hyperglycosylation of

said cytokine, chemokine, growth factor or polypeptide hormone, or antagonist thereof; a pharmaceutical composition comprising the conjugate of claim 38 and a pharmaceutically acceptable carrier or excipient; a kit comprising the pharmaceutical composition of claim 37; a kit comprising the conjugate of claim 38; a kit comprising the conjugate of claim; a kit comprising the pharmaceutical composition of claim 72.

Gaertner et al., teach site-specific attachment of functionalized poly(ethylene glycol) to the amino-terminus of proteins (see entire paper, especially p. 40, column 1, last paragraph to column 2). Monomethoxypoly(ethylene glycol) is taught at p. 38, column 1, first paragraph. PEG-IL-8 is taught at p. 38, column 2, third paragraph. Various molecular weights of PEG are taught in Figures 1-7, including 5 kDa, 10kDa, 20kDa (see pages 41-43). Gaertner et al., do not teach PEG-conjugates of IFNα, IFNβ, EGF, IL-2, growth hormone, IGF-1 or EPO.

Ikeda et al., teach polyethylene glycol derivatives conjugated to proteins (column 3, lines 8-12). Pharmaceutical compositions are taught at column 3, line 15 and column 6, lines 24-26. PEG-conjugates of cytokines including IFNα, IFNβ, IL-2, growth hormone, insulin-like growth factor-1 (see also Example 3, column 9), EPO, and EGF are taught at column 4, lines 52-68 to column 5, lines 1 to 11.Monomethoxypolyethylene glycol is taught at column 6, line 47.

Tutsumi et al., teach PEG-TNF-α (abstract).

Seely teaches a PEG-TNFbp, as a PEGylated TNF antagonist (column 2, lines 1-14). PEGs of varying molecular weights ranging from 0.2 kDa to 100 kDa are taught at column 1, lines 27-28.

Gnanou et al., teach macromonomer synthesis of monohydroxypolyethylene oxide (abstract and p. 2117 second full paragraph).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to combine the teachings of Gaertner et al., with the teachings of Ikeda et al., Tutsumi et al., and Seely in order to conjugate different cytokines, chemokines, and growth factors with various polyalkylene glycol derivatives. Gaertner et al., successfully taught amino-terminus attachment of PEGs to IL-8 and other cytokines. Ikeda et al., taught PEG-conjugates of cytokines, including IFNα, IFNβ, IL-2, growth hormone, IGF-1, EPO, and EGF. Tutsumi et al., successfully taught conjugation of a PEG-TNFα. Seely taught the successful construct of PEG-TNFbp, as a PEGylated TNF antagonist. Substitution of monohydroxypolyethylene oxides in place of monomethoxypolyethylene glycol would have been obvious to one of skill in the art because Gnanou et al., taught that quantitative yields can be obtained under conditions mild enough to prevent polymerization of the unsaturated function. The person of ordinary skill in the art would have been motivated to make the modifications because it would have been obvious to use similar conjugation techniques to create PEG-conjugates of species of related

cytokines and/or cytokine antagonists for pharmaceutical use in treatment of various disorders. Further, because biological function of PEGylated conjugates are dependent on the coupling techniques used, the substitution of monohydroxypolyethylene oxides taught by Gnanou et al., would have been obvious because the monohydroxypolyethylene oxides could be synthesized under mild conditions. The person or ordinary skill would have reasonably would have expected success because biological function of the monohydroxy-PEGylated conjugates would be maintained under mild coupling conditions.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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